BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 10/813,760
Filing Date: March 31, 2004
Appellant: Joel E. Bernstein

Alice O. Martin
For Appellant

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**REPLY BRIEF**

This is in response to the Examiner's Answer mailed March 31, 2010.

**The Examiner Has Not Successfully Rebutted Teaching Away of the Present Invention Based on the Totality of the Prior Art**

In part, Appellant's claimed invention relates to a composition consisting essentially of one or more compounds at doses known to be hepatotoxic combined with methionine and nicotinamide in a pharmaceutically acceptable carrier. As Appellant emphasized on pages 7-9 of the Appeal Brief, Kroger (1999) specifically teaches away from the use of one of Appellant's claimed elements (nicotinamide) in an animal model of drug-induced hepatotoxicity. Accordingly, Kroger (1999), as part of the totality of the prior art, strongly discourages a skilled artisan from using nicotinamide for drug-induced hepatotoxicity and thus qualifies as ***"strong evidence of unobviousness"*** according to MPEP § 2145.

According to MPEP § 2145, the ***totality*** of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is ***"strong evidence of unobviousness."*** *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) (*emphasis added*). Moreover, as stated in the recent *KSR* decision, "when prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." (*KSR International Co. v. Teleflex Inc.*, 550 US 398, 82 USPQ2d 1385, 1395 (U.S. 2007). Therefore, Appellant's invention as defined by the claims cannot be rendered obvious under 35 U.S.C. § 103 if the totality of the prior art teaches away from the invention. Kroger (1999) was published by the same author as the primary reference in the Examiner's obviousness rejection (i.e., Kroger (1997)) and was submitted to the Office by the Appellant in a Supplemental IDS filed October 20, 2008. Accordingly, Kroger (1999) is included in the totality of the prior art and, thus, must be considered in any rejection for obviousness.

On pages 13 and 14 of the Examiner's Answer, the Examiner asserts that:

> In response to applicant's argument that the examiner neither refuted nor responded to the teaching of Kroger et al. 1999 publication, the examiner likes to point out that applicant has received an action on the merits for the originally elected invention, Group I along with an acetaminophen as the hepatotixc *(sic)* compound (Response filed 2/28/2007). Accordingly the search and examination have been only extended to an acetaminophen alone in combination with methionine and nicotinmaide *(sic)*. Contrary to the merits of the case, Kroger'99 reference discussed the activity of methionine and/or nicotinamide in reducing essentially the liver toxicity of methotrexate. Although acetaminophen is disclosed in the toxicity study, a lower dose (50mg/kg) utilized in the study is not known to cause hepatotoxicity as seen in the Table 3 (as well as line 3 of the abstract). Kroger '99 discloses that mice were given 50mg/kg acetaminophen, which itself has no effect on the liver.

The Examiner goes on to concede that:

> As discussed in preceding comments, the examiner's search and examination have not been extended beyond acetaminophen. Thus, the examiner has not (fully) considered Kroger'99 references since it is premature to discuss about non-elected species, methotrexate.

Finally, in regards to the teachings of the Kroger (1999) reference, the Examiner states that:

> There is no conclusive evidence indicated in Kroger'99 that nicotinamide is non-hepatoprotective at high dosage and that at lower dosage nicotinamide increases liver damage from the acetaminophen.
>
> Even assuming arguendo that Kroger'99 is relevant to the merits of the case, Table 5 discloses that with increasing [nicotinamide] doses, there is a reduction in GOT and GPT activities. Thus, coupled with the result of Table 4, one having ordinary skill in the art would have perceived that the simultaneous administration of either nicotinamide or methionine or both together would be useful in reducing the liver toxic effect of methotrexate, more broadly other drugs at does known to be hepatotoxic, e.g., acetaminophen (citation omitted).

Contrary to the statements in the Examiner's Answer, Kroger (1999) is relevant prior art to Appellant's claimed invention. As Appellant argued on page 7-9 of the Appeal Brief dated January 4, 2010, "[t]he data in the Kroger et al 1999 reference teaches the *direct opposite* of the present application regarding nicotinamide's protective effects." (*emphasis added).* Due to the teaching away of the present invention based on the totality of the prior art, the Board should find that the Examiner's rejection under 35 U.S.C. § 103 does not render claims 1-3, 5-9, and 11-15 obvious.

Kroger (1999) utilizes a mouse model of drug-induced hepatotoxicity in which acetaminophen and methotrexate are given to "induce damage of the liver." (see Kroger (1999), page 203, first full paragraph). Although acetaminophen was administered in lower doses compared to Kroger (1997), co-administration of acetaminophen with low doses of methotrexate resulted in hepatotoxicity as demonstrated by elevated levels of hepatic enzymes (see Kroger (1999), Table 3). Thereafter, nicotinamide was administered in combination with acetaminophen and methotrexate in an attempt to prevent the drug-induced hepatotoxicity.

As stated on page 8 of the Appeal Brief, Table 5 of Kroger (1999) teaches away from the elements of Appellant's claimed invention. For the Board's convenience, Table 5 of Kroger (1999), which describes the results of administering nicotinamide (NA) in combination with acetaminophen (PAR) and methotrexate (MTX), is presented below.

Table 5
Toxicity in mice after application of MTX, acetaminophen, and NA, respectively

| Treatment | GOT | GPT |
|---|---|---|
| NaCl | 50.23 ± 9.69 (6) | 34.25 ± 6.44 (6) |
| MTX, 50 mg/kg | 69.75 ± 14.76 (6) | 47.85 ± 11.90 (6) |
| MTX, 50 mg/kg, + PAR, 50 mg/kg[a] | 106.17 ± 9.47 (3) | 65.23 ± 13.57 (3) |
| MTX, 50 mg/kg, + PAR, 50 mg/kg, + NA, 50 mg/kg | 187.12 ± 94.37 (6) | 83.82 ± 31.40 (6) |
| MTX, 50 mg/kg, + PAR, 50 mg/kg, + NA, 100 mg/kg | 95.48 ± 34.38 (6) | 69.48 ± 25.59 (6) |
| MTX, 50 mg/kg, + PAR, 50 mg/kg, + NA, 250 mg/kg | 97.50 ± 64.90 (5) | 64.24 ± 24.04 (5) |

Note: MTX, NaCl, and NA were applied intraperitoneally over 4 days. Then the animals were starved for 18 h. After this period, MTX, NaCl, and NA were given again. Additionally, the animals received acetaminophen (PAR) by gavage. Blood was taken 16 h later. Number of animals in parentheses.

[a] Three animals died.

Specifically, Table 5 of Kroger (1999) shows that administering 50 mg/kg of nicotinamide in combination with acetaminophen and methotrexate demonstrated **increased** liver toxicity compared to acetaminophen and methotrexate administered alone. Furthermore, administering higher doses of nicotinamide (e.g., 100 mg/kg or 250 mg/kg) in combination with acetaminophen and methotrexate was **non-hepatoprotective** compared to acetaminophen and methotrexate administered alone. Consequently, as clearly explained in the Appeal Brief, a skilled artisan would be strongly discouraged by Kroger (1999) from using nicotinamide in a drug-induced hepatotoxicity model including acetaminophen due to the ineffective and counterproductive effects of nicotinamide in mitigating hepatotoxicity.

The Examiner's Answer fails to address or acknowledge in sufficient detail that Kroger (1999) teaches away from Appellant's claimed invention. In fact, the Examiner admits that he "has not (fully) considered" the Kroger (1999) reference. This admission is contrary to the provisions of MPEP § 2145, which states that "the ***totality*** of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is ***"strong evidence of unobviousness."*** (emphasis added).

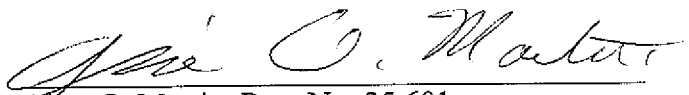
Moreover, in the limited analysis contained in the Examiner's Answer, the Examiner appears to have mischaracterized the teachings of Kroger (1999) as a teaching prior art reference. On page 14 of the Examiner's Answer, the Examiner states that "[t]here is no conclusive evidence indicated in Kroger'99 that nicotinamide is non-hepatoprotective at high dosage and that at lower

dosage nicotinamide increases liver damage from the acetaminophen." On the contrary, as stated on page 8 of the Appeal Brief and as shown in Table 5 of Kroger (1999), low doses of nicotinamide administered with acetaminophen and methotrexate resulted in **substantially elevated hepatic enzyme levels** (i.e., **increased liver damage**) compared to administration of acetaminophen and methotrexate alone. Furthermore, higher doses of nicotinamide administered with acetaminophen and methotrexate resulted in **comparable hepatic enzyme levels** (i.e., **no protection of liver damage**) to those observed following administration of acetaminophen and methotrexate alone. Accordingly, Table 5 of Kroger (1999) demonstrates conclusive evidence to a skilled artisan that administering nicotinamide in a drug-induced hepatotoxicity model would be of no benefit for the prevention or treatment of liver damage.

Furthermore, a careful reading of Kroger (1999) demonstrates to a skilled artisan that the administration of nicotinamide in a drug-induced hepatotoxicity model would be inherently risky to the administered animal. Indeed, administering nicotinamide to mice in combination with acetaminophen and methotrexate resulted in the ***death of three of the six animals*** (see Kroger (1999), page 205, first sentence of section 2.5). Upon reading Kroger (1999), a skilled artisan would undoubtedly be hesitant to administer a combination of drugs that had been shown to result in the ***death of 50% of the study population***. Accordingly, Kroger (1999) teaches away from the use of nicotinamide in a model of drug-induced hepatotoxicity containing acetaminophen due to the risk of death of subjects treated with the combination.

In summary, Kroger (1999), as part of the totality of the prior art for the present application, strongly discourages a skilled artisan from using nicotinamide for drug-induced hepatotoxicity and, thus, is strong evidence of unobviousness of Appellant's claimed invention. Allowance of claims on appeal is requested.

Respectfully submitted,



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